UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/034,950	12/26/2001	Bhami Shenoy	VPI/00-08	9344

1473 7590 05/15/2006

FISH & NEAVE IP GROUP
ROPES & GRAY LLP
1251 AVENUE OF THE AMERICAS FL C3
NEW YORK, NY 10020-1105

EXAMINER	
NOAKES, SUZANNE MARIE	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 05/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/034,950	SHENOY ET AL.	
	Examiner	Art Unit	
	Suzanne M. Noakes, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *84-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *84-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Applicants should note that both the location and the examiner of the instant application has changed. AU's 1653/1656 will be prosecuting the instant application (1656 is a protein crystallography AU).

2. The amendments filed by Applicants 13 February 2006 has been entered and is acknowledged. Claims 1-83 have been cancelled and new claims 84-91 have been added.

Response to Arguments

3. Applicant's arguments have been fully considered and are persuasive. All previous rejections are hereby withdrawn. However, upon further consideration, new ground(s) of rejection are made below.

Claim Rejections - 35 USC § 112 –2nd paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 86-91 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: The leap from crystals produced from micro-batch in step c of claim 86 to that of crystals produced by the large-batch crystallization is incomplete and/or unclear. For instance, are the crystals in step c used

to seed the large-scale crystallization in step d as is described in Examples 1-8, 13-27 and 31-33? Or are new *de novo* crystals formed in the scaled up version of steps d and e simply by using the same protein concentration and buffers used in the micro-batch crystallizations?

6. Claim 85 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "about 20 mg/ml" in claim 85 is a relative term which renders the claim indefinite. The term "about" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term is rendered indefinite because about is a subjective term and in this case could mean 1 mg/ml to one skilled artisan but 5-10 mg/ml to another. Thus, the metes and bounds of the claimed invention are not defined.

Claim Rejections - 35 USC § 112 – 1st paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 84 and 85 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for crystals of Infliximab produced by very specific crystallization methods and conditions, does not reasonably provide enablement for crystals of Infliximab above or beyond what is described in the specification, or a

process that produces just any antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to crystals of Infliximab. However, the specification *only* sufficiently describes crystals that have been produced by the specific protein and buffer conditions and the technique of microbatch, described in Examples 34-37. Beyond this scope, the specification is void of any other examples of how a skilled artisan would be able to produce Infliximab crystals with any success. Furthermore, the specification clearly states that the prior art has shown that attempts have been extremely difficult and unsuccessful in crystallizing whole antibodies. Thus, a skilled artisan, in order to achieve that which is claimed, would be required to determine *de novo* crystallization conditions in order to make and/or use the claimed invention. In this case, the burden is seen as undue when the Wands analysis is considered.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many

factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

In the instant case, the quantity of experimentation would be considerable because the smallest change in ***any*** parameter in crystallizing a protein/antibody can have enormous consequences. Thus, it is not enough to have the crystallization conditions of a related/similar protein/antibody or 'native' protein/antibody. Rather, what would be required is precise instruction about how to make the each and every crystal (each and every one) in order to avoid undue experimentation. However, there is no direction or guidance in the specification of how a skilled artisan might achieve crystal growth of Infliximab in any other conditions or with any other crystallization techniques (e.g. hanging drop, sitting drop, capillary liquid-liquid diffusion etc.). The nature of the invention and of the prior art suggests that crystallizing proteins is an extremely tenuous science; what works for one protein or antibody does not necessarily for another, and what works for one native protein or antibody does not necessarily work for a mutant or fragment even though they essentially contain the same protein/antibody that has already been crystallized. Specific crystallization conditions (e.g. temperature, buffer, salt, protein concentration etc.) are needed for each protein and/or antibody (see

Weber, Overview of Crystallization Methods. Methods in Enzymology, 1997, Vol. 276, pp. 13-22).

At best, the art of crystallization is unpredictable even to those skilled in the art who may either perform the experiments by hand or who are assisted by automated robotics because it often times requires thousands of individual experiments in order to find the one or two conditions that are successful. Even then, there is no guarantee. It is even a well known fact in the art that luck often times play a fortuitous role in obtaining successful crystallization conditions despite the extremely high skill level of those in the art. For example, Drenth describes a case where it seemed impossible to successfully crystallize a particular protein they were working on until the air conditioner in the laboratory broke down over night thereby increasing the temperature in the lab to the "correct temperature" which was needed to induce successful crystal growth (see Drenth, "Principles of Protein X-Ray Crystallography", 2nd Edition, 1999 Springer-Verlag New York Inc., Chapter 1, p. 19, 4th paragraph, lines 1-2). This is just one example out of the many countless tales of the unpredictability of the art. Every skilled artisan who has worked in the field knows and understands that the art of crystallizing anything is extremely difficult because there are so many variables; and finding the precise combination of variables that leads to successful crystallization is a simply a matter of trial-and-error. Furthermore, the prior art is of little assistance because Infliximab has never been crystallized before. Thus, when all things are considered and the Wands factors are treated on their merits, the claim is not enabled because a great deal of

undue experimentation would be expected and necessary in order to practice the full scope of claimed invention.

9. Claims 86-91 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the large-batch production of Retuximab and Trastuzumab, does not reasonably provide enablement for the production of any other antibody by the same process. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to the process of large-scale crystallization of a genus of antibodies, wherein one claim is drawn to the antibody species Infliximab (claim 90). It is assumed from the claims that once crystallization conditions on a micro-scale have been achieved that this is directly translated successfully into the large-scale production of the same crystals. However, the art of crystallizing anything, as described above is incredibly unpredictable. Thus, in order for a skilled artisan not to be imposed with the burden of undue experimentation, they must have in hand, the exact protein they are working with, the exact crystallization conditions (e.g. temperature, protein concentration, buffer concentration, crystallization method utilized, etc.) that work for the micro-scale techniques and the exact conditions for the scaled up large-batch crystallization conditions. Anything less will implicitly impart undue experimentation upon a skilled artisan because the art is so highly unpredictable.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988) and are described above in Section 7.

Clearly the enablement requirement is predicated upon not imposing any undue experimentation upon a skilled artisan. However, in the instant case, Applicants have sufficiently described in the specification a large scale batch crystallization method that is successful only for the antibodies Retuximab and Trastuzumab (see Examples 1-8, 13-27 and 31-33). In each case, the temperature, buffer, salt, protein concentration and method of crystallization have been sufficiently described in the specification (not the claims however) for both of the micro-scale and large-scale crystallization procedures. However, because the scope of the claims far exceeds what is actually being claimed, undue experimentation will be expected because the claims as written cover every single antibody in existence and the specification does not describe or offer support for this magnitude scope. Thus a skilled artisan would have to necessarily devise *de novo* crystallization conditions, first on a micro-scale level followed by *de novo* conditions on scaled-up leverl, in order to practice the claimed invention. And as Applicants correctly point out in their specification, crystallizing antibodies is and has been a very difficult task: "Although crystallization of whole antibodies has been a subject of significant interest for the last three decades, very few whole antibodies have ever been crystallized and, even then, solely in the context of structural studies." (see p. 5, paragraph [0010]). Thus the prior art is of no use to the applicability and success of the present invention for just getting to step b or c of claim 86. Even *if* a skilled artisan was

able to achieve *de novo* crystallization conditions, further undue experimentation would be expected in devising successful conditions for crystal growth in the scaled-up large-scale batch methods because knowing the crystallization conditions of the micro-batch method does not directly translate to successful crystallization on a scaled up version. This is a known problem in the art and Jen et al. (Pharm. Res. 2001, 18(11):1483-148), who teach an overview of the success over the years of producing protein crystals on a large scale for the use in pharmaceuticals, specifically state the following (p.1487, 1st column, 2nd paragraph):

> "Once a crystal candidate has shown promising properties for pharmaceutical development, the crystallization effort must be up-scaled. The batch and dialysis methods are likely the easiest options for adaptation to large-scale crystallization because similar constructions already exist for chemical, pharmaceutical, and biotechnological processes. *The conversion of microliter-size crystallization trials into industrial dimensions, however, may be a challenging task*. Successful upscaling requires careful documentation and understanding of favorable conditions found during the screening process, optimally defined in terms of particle shape, size, and solubility (degree of saturation). The size and shape of the products from production trials would indicated which operating factors, such as protein and precipitation concentration, could be adjusted to achieved the desired product. Once the operating parameters have been optimized, crystal form and size can be used to monitor product quality."

Thus, the overall process is as claimed will necessarily and inherently impose undue experimentation upon a skilled artisan despite the high level of skill in the art because of the unpredictability which is intrinsic in the art of crystallizations.

Thus, when all things are considered and the Wands factors are treated on their merits, the claim is not enabled because a great deal of undue experimentation would be expected and necessary in order to practice the full scope of claimed invention.

10. Claims 90 and 91 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a process of producing Infliximab crystals by a large-batch crystallization method and crystals produced thereof. However, nowhere in the instant disclosure is it ever described, the conditions used to actually produce crystals by this technique. Every example given is drawn to micro-batch crystallization and as described above, just because one may have those conditions at hand, does not mean that this will translate into success in large-scale methods. Thus, it is expected that undue experimentation would be imposed on a skilled artisan in order to make and use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988) and are described above in Section 7.

As stated above, the leap of going from micro-scale crystallizations to macro-scale is one that is not necessarily straight forward and is very unpredictable. Jen et al. specifically state: "The conversion of microliter-size crystallization trials into industrial dimensions, however, may be a challenging task." Thus, the quantity of experimentation would be considerable because the smallest change in ***any*** parameter in crystallizing a protein/antibody can have enormous consequences. And since the

specification does not describe anywhere, the large-scale batch process for the production of Infliximab crystals, a skilled artisan would necessarily have to experiment unduly in order to make and use the invention as claimed. It is not enough to have the crystallization conditions on the micro scale, what is needed is the crystallization conditions on the macro scale as well in order to comply with the enablement requirement in this case.

Written Description:

11. Claims 84 and 85 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to a broad genus of any crystal of Infliximab (claim 84) or one that is pharmaceutical composition (claim 85). While the structure and function of some species of said genera of Infliximab crystals are disclosed in the specification, the common characteristics of the species that define said genera are not described.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original).

To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).

The specification fully describes four species of Infliximab crystals that are produced by the microbatch method with slightly different conditions that fall within the instant genera of crystals. Examples 34 and 35 describe the precise antibody resuspension buffer and the exact crystallization conditions which results in rod shaped crystals, Example 36 varies slightly in the buffers and lack of agitation and results in cubed shaped crystals and finally, Example 37 varies the protein concentration and buffers used and results in star shaped crystals (see pp. 98-99). All of these Examples sufficiently and full describe species of Infliximab crystals. However, these species do not sufficiently describe the entire genus of Infliximab crystals.

In general, for a species of crystal to be adequately described, the following must be adequately disclosed in the specification and the claims: (1) the composition of the crystal (exact structural features of all molecules in the crystal must be described, including the protein/antibody (preferably a SEQ ID NO of all included residues) and any molecule bound to it) (2) the exact protein concentration and buffer the protein/antibody

is in, (3) the exact temperature, buffers, salts, additives used for crystallization and 4) the technique used to obtain the crystal (e.g. vapor diffusion, microbatch, liquid-liquid diffusion, etc). The four species noted above have adequately met this burden. However, the process of obtaining the crystals which is encompassed by the breadth of the claims is not described. A singular chemical composition can crystallize differently based on the crystallization conditions and techniques used. For example, if a skilled artisan wants to crystallize Infliximab for structural studies, then the crystallization technique, buffer considerations, temperatures, etc. are going to very different than trying to crystallize a protein/antibody for therapeutic use because the overall objectives are so different and the quality of the crystals are important. Applicants even note this major difference in their specification on p. 6.

Based on the instant the specification, the chemical composition, the process of obtaining Infliximab crystals and quality of the crystals produced encompassed by the breadth of the claims is unpredictable to one of skill in the art. One of skill in the art would be unable to predict the structure of other members of the genera by virtue of the instant disclosure. Therefore, claims drawn to the instant genera of Infliximab crystals also are not adequately described.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claim 85 is rejected under 35 U.S.C. 102(b) as being anticipated by Cheetham et al. (JMB, 1998, 284:85-99).

The claim is directed to a pharmaceutical composition comprising an antibody with a concentration greater than about 20 mg/ml.

Cheetham et al. teach the crystallization of Rat Anti-CD52 (CAMPATH-1) therapeutic antibody Fab fragment which is crystallized in a pharmaceutically acceptable buffer at 20 mg/ml (see CAMPATH-1G, p.88, Table 1). Thus the antibody crystal in its mother liquor constitutes a pharmaceutically acceptable composition that has a crystal of an antibody that is about 20 mg/ml. Because the term "about" is rendered indefinite as described above in Section 6 of this Office action, the fact that the crystallization takes place at 20 mg/ml meets the limitation of the claims because its greater than about 20 mg/ml, which could mean less than 20 mg/ml.

Conclusion

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzanne M. Noakes, Ph.D. whose telephone number is 571-272-2924. The examiner can normally be reached on Monday to Friday, 7.30am to 4.00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisors, Jon Weber or Kathleen Kerr can be reached on 571-272-0925 or 571-272-0931, respectively. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SMN
12 May 2006

KATHLEEN M. KERR, PH.D.
SUPERVISORY PATENT EXAMINER